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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,253	01/24/2002	Rosana Kapeller-Libermann	35800/242128(5800-62B)	9314

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/056,253	KAPELLER-LIBERMANN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ 1/24/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a continuation of 09/443,795, now US Patent 6,383,780.

Claims 1-11 are pending and under consideration in this Office Action.

Information Disclosure Statement

An information disclosure statement was received and entered on 1/24/02. Citation numbers 2, 3, 6, 13, 14, and 19 are incomplete because they lack publication dates. These references were considered, but cannot be published as citations unless they are corrected. Submission of a corrected IDS is suggested.

Claim Objections

Claims 3, 6, and 10 are objected to. Claim 3 is ungrammatical because it is unclear what is the relationship between, "the group" and items (a-c) that follow. Insertion of the words, "consisting of" immediately after "the group" is suggested. Claims 6 and 10 contain in item (b) "bya" which is not a word. Insertion of a space to yield the words "by" and "a" is suggested.

Drawings

The drawings filed 1/24/02 are acceptable for the purpose of examination.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 4, line 24, page 8, line 25 discloses amino acid equences in excess of 3 amino acids that are not accompanied by a SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to reflect this, if these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,383,780. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

US Patent 6,383,780 contains claims drawn to isolated nucleic acids comprising SEQ ID NO:2, (claims 1-9) methods of making the encoded protein (claims 4 and 9), and methods of detecting nucleic acids using SEQ ID NO:2 (claims 5-7). The instant claims embrace these embodiments as they are drawn to nucleic acids comprising

variants and fragments of SEQ ID NO:2, and to methods of making encoded proteins and detecting nucleic acids. Because SEQ ID NO:2 is a species of each of the instantly claimed genuses of nucleic acids, the claims of '780 render the instant claims obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-11 are directed to nucleic acids encoding a polypeptide with any aminopeptidase activity, wherein the nucleic acid comprises either at least 500 contiguous nucleotides of SEQ ID NO:2, or is at least about 80, 85 or 90% identical to SEQ ID NO:2.

SEQ ID NO:2 is an aminopeptidase B (ApB). The prior art teaches that these enzymes catalyze the removal of N-terminal arginine and lysine residues. See Fukasawa et al (J. Biol. Chem. 271(48): (1996), page 30731, column 1, lines 5-10).

A wide variety of aminopeptidases is known in the art, and these enzymes catalyze different reactions. For example, the specification exemplifies amino peptidases that remove N-terminal methionines as well as aminopeptidases that are specific for arginine, leucine, and D-amino acids (see page 2, lines 9-14). It is clear to those of ordinary skill in the art that the specificity of a given aminopeptidase is dependent on its structure. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As such one of skill in the art could not conclude that Applicant was in possession of the genus of polypeptides comprising either at least 500 contiguous nucleotides of SEQ ID NO:2, or about 80, 85 or 90% sequence identity to SEQ ID NO:2, ***and*** the ability to cleave any N-terminal amino acid from any polypeptide. This rejection can be overcome by amending the claims to require of the enzyme an aminopeptidase that has the aminopeptidase activity of the polypeptide of SEQ ID NO:1.

Enablement

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding fragments of the amino acid sequence of SEQ ID NO:1, wherein the fragments have the amino peptidase activity of SEQ ID NO:1, does not reasonably provide enablement for nucleic acids encoding sequence variants of SEQ ID NO:1, or sequence variants of fragments of SEQ ID NO:1, wherein the variants have any aminopeptidase activity broadly. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-11 are drawn to nucleic acids encoding variants of the amino acid sequence of SEQ ID NO:1 in which the nucleic acid sequences must be are 85, 90, or 90% identical to the nucleic acid sequence of SEQ ID NO:2. SEQ ID NO:2 is a 2459 nucleotides in length, so the claims allow 369 (85%), 246 (90%), or 123 (95%) nucleotide alterations in SEQ ID NO:2. SEQ ID NO:1 is a polypeptide of 650 amino acids. If each of nucleotide alteration occurred in the second base of a codon in the open reading frame of SEQ ID NO:2, then the resulting polypeptides would be only 43%, 62%, and 81% identical to SEQ ID NO:1, respectively.

The prior art teaches a polypeptide, rat aminopeptidase B, that is 88.6% identical to SEQ ID NO:1. See Fukasawa et al (J. Biol. Chem. 271(48): (1996). Fukasawa et al (Biochem J. 339: 497-502, 1999) taught that aminopeptidase B is a zinc metalloprotease comprising a characteristic $HEXXHX_{18}E$ zinc binding motif. Fukasawa showed that mutations in this region can interfere with catalysis. Specifically, H324Y, E325A, H328Y, and E347A mutations inactivate the aminopeptidase, whereas S327A decreases catalysis by about 15%. Y408F, N409S, and N409S/E410S mutations are not located in the active site but interfere with catalysis without completely inactivating the enzyme. See e.g. Table 2 at page 499. The specification identifies three active site segments, KKK from positions 161-163, the $HEXXHX_{18}E$ motif from 325-348, and a KGFCFVSYL moiety from 418-425. The rationale for the assignment of the KKK and

KGFCFVSYL sequences as active site regions is unclear as these are identified by the prosite analysis in Fig. 4 as an amidation site and a putative RNA binding region, respectively. The specification provides general guidance as to what amino acid substitutions are deemed conservative in Table 1 at page 13 of the specification. No specific guidance is provided with regard to what specific amino acid substitutions are allowed at which positions, and no working example of any substitution mutation is provided. So, the prior art identifies as many as 20 single positions that can be mutated without eliminating catalysis, and one mutation in which 2 positions can be changed simultaneously, providing support for the position that at least 0.3% (2/650) of the amino acid positions in the protein can be simultaneously altered without eliminating aminopeptidase activity. In contrast, the instant claims would allow as much as 57% of amino acids to be altered simultaneously.

The prior art teaches that the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it

would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the cited art indicate that the effects of mutations on protein structure are unpredictable and must be determined empirically. The prior art provides limited specific guidance as to which residues of an aminopeptidase B can be substituted and which cannot, but the few residues for which there are data fall far short of the extensive modifications that are embraced by the instant claims.

It interesting to note that Fukasawa (1999) recognized a high degree of homology between rat aminopeptidase B (ApB) and leukotriene A4 hydrolase (LTA4), an enzyme with both aminopeptidase and epoxide hydrolase activities. However, despite the fact that rat ApB was more closely related to LTA4 than to any other aminopeptidase family member, Fukasawa showed that rat ApB had no epoxide hydrolase activity. Furthermore, when site directed mutations were made to the rat ApB to render it more similar to LTA4, these changes failed to produce epoxide hydrolase activity in the resulting enzymes. This provides further evidence of the unpredictability of protein structure/function relationships.

Finally, the claims broadly encompass nucleic acids encoding polypeptides with **any** aminopeptidase activity. As noted above under Written Description, the prior art teaches that aminopeptidase B enzymes catalyze the removal of N-terminal arginine and lysine residues, whereas there are many other aminopeptidases that have different specificities owing to different three-dimensional structures. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As noted above the relationship between protein structure and function is complex and unpredictable. Absent guidance in the specification , one of skill in the art could not make fragments and variants of SEQ ID NO:1 that provide aminopeptidase activity other than that comprised by SEQ ID NO:1, without undue experimentation.

In view of the unpredictable nature of the protein structure/function relationships in general, the scarcity of data concerning aminopeptidase B structure and function, the lack of guidance or working examples in the specification regarding which amino acid residues can be substituted and which cannot while preserving aminopeptidase activity, and the lack of guidance concerning how to confer aminopeptidase SEQ ID NO:1 fragments and variants other than ApB activity, one of skill in the art could not make the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 10, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Robison et al (US Patent 6,331,427, issued 12/18/01.

Robison teaches that SEQ ID NO:11 encodes a zinc protease. This sequence is 83.4% identical to SEQ ID NO:2, and comprises 1206 contiguous bases from positions 883-2088 that are identical to bases 1252-2457 of SEQ ID NO:1 (see attached sequence alignment. Robison also teaches methods of using the sequence to express the encoded polypeptide and detect nucleic acids in a sample. See column 1, lines 48-51, column 2, lines 20-22, and 34-41, column 14, lines 16-42, and columns 65-68.

Thus Robison anticipates the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the

hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at 703-306-3217. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.